REMARKS

Reconsideration and continuing examination of the above-identified application is respectfully requested in view of the amendments above and the discussion that follows.

Claims 21-26, 28-29 and 52-57 are in the case and are before the Examiner.

A. Rejections Under 35 USC §103

1. Claims 21-23, 25, 52, 54 and 56

Claims 21-23, 25, 52, 54 and 56 were rejected as allegedly obvious from the combined teachings of Bergh et al. US Patent No. 4,925,796) in view of Prieels et al., *J. Biol. Chem.* **256(20):**10456-10463 (1981) and Schachter et al., *Methods Enzymol.* **28**:285-287 (1972). The Action notes that Bergh teaches the use of a fucosyltransferase as disclosed by Prieels and GDP-fucose to carry out a fucosylation reaction, while omitting a disclosure of a GDP-fucose forming enzyme, fucose kinase and GDP-pyrophosphorylase. The Action asserts that Schachter teaches enzymatic preparation of the GDP-fucose needed by Bergh. The action concludes that based on these disclosures, a worker of ordinary skill would have combined the enzymes and substrates to arrive at the claimed subject matter. This basis for rejection cannot be agreed with and is respectfully traversed.

The Action thus argues that each of the recited claim elements was disclosed separately in the art, and because each was known, it would have been obvious to put them together as is claimed here. On the other hand, the file of this application and its immediate predecessor contain a Declaration executed on

November 08, 2004 by a pre-eminent worker in this field, Dr. James Paulson, a lead author whose work is cited in the relied-on Bergh patent. Dr. Paulson there pointed out that the enzymes involved here do not naturally occur in the same cellular compartment, nor do they act in the same cellular compartment, and that one of the enzyme products, GDP-fucose, gets transmitted back and forth between the Golgi and cytoplasm where those enzymes work in their natural environment. That based on those facts and because of the differences between cellular and *in vitro* manufacture of fucosylated products, Dr. Paulson opined that "the worker of ordinary skill at the time the claimed invention was made would have been more likely to expect interference between the enzymes, reactants and products than a lack of such interference and therefore would have required direct evidence of a lack of interference." (Paulson Paragraph 15).

The present and prior Actions attempted to refute Dr. Paulson's points by noting that the enzymes are active at the same pH value and temperature. That statement is correct for the recited enzymes, as it is for the vast majority of enzymes in the body except for those found in the gut, but it does not refute the fact pointed out by Dr. Paulson that the enzymes naturally exist in different areas of the cell.

A further illustration of that fact is shown in the pages from Chapter 17 of Molecular Cell Biology attached as Exhibit A. Thus, the first full paragraph on page 713 of Exhibit A notes that "[a]ll known glycosyltransferases that act on secretory proteins are integral membrane proteins with active sites facing the lumen [inside] of the organelle." The last paragraph on that page states "[a]ll the sugar nucleotides used in the synthesis of glycoproteins and glycolipids are made in

the cytosol from nucleoside triphosphates and sugar phosphates." Figure 17-33 on page 715 illustrates those statements by showing the nucleoside-diphospho sugar (fucose) molecules such as GDP-Fuc coming into the Golgi where glycosyl transfer takes place and the monophosphonucleoside reaction product leaving the Golgi.

The last sentence of the first paragraph of page 718 notes that the three regions of the Golgi have different "enzymes that introduce different modifications to secretory and membrane proteins; thus each region in effect functions as a distinct organelle." The text of Exhibit A thus indicates that the enzymes in different portions of the same organelle cause those regions to function as distinct organelles, those enzymes are all within the Golgi membranes with active sites pointing inwardly, and the nucleoside-diphospho fucose forming enzyme is on the other side of the Golgi membrane in the cytosol. Thus, Nature has separated the different glycosyltransferases and separated all of those transferase enzymes from the enzyme that forms their nucleoside-diphospho fucose reactant. None of the relied-on teachings places the enzymes together, and none teaches use of a catalytic amount of the nucleoside-diphospho sugar forming enzyme.

It is submitted that it is incorrect to assert that mere recitation of the enzymes in the art is sufficient to find obviousness when the art knew so much more about the enzymes, their locations and functions. At best, the art might make the claimed combination "obvious to try". The law requires a likelihood of success to transform that which might be "obvious to try" into to that which is obvious under In re O'Farrell, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988), and Dr. Paulson's

Declaration points to the lack of such a likelihood. This basis for rejection should be withdrawn.

The Action continues to rely on the Prieels paper that reported isolation of an α1,3/4-fucosyltransferase from human milk. It is reiterated that although an active enzyme was found in human milk, no activity within the milk has been established or even asserted in the Action for that enzyme. That is, the fact that an active enzyme is present in milk in no way implies that that enzyme reacts with a substrate in the milk.

Thus, the ability to obtain an active enzyme from human milk only illustrates that fact, an active α1,3/4-fucosyltransferase is present in and extractable from human milk. That teaching says nothing more about the claimed combination of that enzyme with a nucleoside-diphospho fucose forming enzyme than finding the enzyme to be available in the Sigma Chemicals catalog. The point again is that that enzyme is active in the inside of Golgi, whereas the other recited enzyme is active outside the Golgi in the cytosol.

The Action continues to read the out of context words of the art, taking as much as is needed to form a sum that includes the claimed subject matter, while discounting evidence of a world-recognized expert. That expert stated that a skilled worker at the time the parental application was filed would have no way to know if the enzymes and their respective substrates were compatible with each other in an *in vitro* environment until someone tried to put them together (Paulson Paragraph 16). The evidence in this record further holds that motivation for putting the enzymes together was not intuitive and there was only hindsight motivation for a worker of ordinary skill to

combine the relied-on teachings as had been done (Paulson Paragraph 17).

Of course, when one looks at what was done by other workers of skill in this art prior to Dr. Wong's publications, one sees that no one put these enzymes together even though they were available. Schachter had his enzymes in 1972 and Prieels had his in 1981. Thus, it took about twenty years from the Schachter work and about ten years from Prieels for Dr. Wong to do what was so blatantly obvious from the asserted motivation to combine.

It is submitted that when the materials were as readily available as has been asserted, and the claimed invention was as obvious as has been asserted, someone would have done what Dr. Wong did long before he did it. The fact is no one did it. The Action counters by relying on the holding of *In re Wright*, 193 USPQ 332 (CCPA 1977) to the effect that the age of cited art is not of import to a lack of obviousness without a showing that the art tried and failed.

That holding was made in *Wright* under a different set of facts in which the finding of obviousness was ultimately based on a single teaching. That fact notwithstanding, it is submitted that each relied-on teaching of record that shows use of one or the other of the recited enzymes alone and not present together as claimed is evidence of such a failure of the art.

None of the relied-on art teaches an *in vitro* system that places together an isolated glycosyltransferase and a catalytic amount of an isolated enzyme that forms a nucleoside diphosphate sugar substrate for the transferase as is here claimed. One cannot logically prove non-existence. However, the absence of facts is itself evidence that a combination of teachings that was supposed to be so facile and made with such

apparent motivation but never existed in the literature was not as appropriately combined as one might have at first thought. Although seemingly simple, the workers of ordinary skill never put this invention together because they could not look backwards and say that since it was done, it was obvious to have done it. Thus, again, the Action has improperly reconstructed the claimed subject matter through hindsight based on the teachings of the application itself, and this basis for rejection should be withdrawn.

2. Claims 21-25, 52, 54, 55 and 57

Claims 21-25, 52, 54, 55 and 57 were rejected over the Bergh, Prieels and Schachter disclosures as applied above, and further in view of the teachings of Demain et al. US Patent No. 4,178,210. This basis for rejection cannot be agreed with and is respectfully traversed.

The deficiencies of the tripartite Bergh, Prieels and Schachter disclosures have been discussed as they apply to the present claims. As such, adding an out of context disclosure concerning the well-known ATP regenerating system that Demain used to boost production of a cephalosporin provides nothing more to the tripartite disclosures in regard to the independent claims and therefore cannot make obvious the claims that depend from those unobvious independent claims.

It is reiterated that an ATP regenerating system is not recited in the claims at issue here. Indeed, ATP is not mentioned in these claims. That ATP can be used to prepare fucose-1-phosphate is not relevant to these claims that do not recite that method of preparation. That is not to say that ATP cannot be present, but rather that it is not recited in the claims, nor is it needed. The Examiner's attention is again

invited to Schemes 12 and 13 at pages 43 and 45 on this point. It is there shown that the kinase recited in the claims is used to form GTP and then GDP-Fuc.

To rely on a disclosure that recites an ATP regenerating system to augment the Bergh or Schachter disclosures to make them operable because "Schachter's process requires ATP…", only underscores the inapplicability of those disclosures to these claims, and the patentability of these claims over those disclosures. It is again submitted that this basis for rejection should be withdrawn.

3. Claims 21-26, 28, 29 and 52-57

Claims 21-26, 28, 29 and 52-57 were rejected over the Bergh, Prieels, Schachter and Demain disclosures as above further in view of the teachings of Yamamoto et al., *Agric. Biol. Chem.* **48(3)**:823-824 (1984). This basis for rejection cannot be agreed with and is respectfully traversed.

The previous discussion has illustrated the inappropriate basis for rejection provided by the combination of the Bergh, Prieels, Schachter and Demain disclosures. The addition of the Yamamoto teachings to provide the isolated disclosure of converting GDP-mannose into GDP-fucose cannot make the otherwise unobvious independent claims obvious, nor can those disclosures make obvious the claims that depend from those unobvious independent claims. It is thus submitted that this basis for rejection be with drawn.

It is noted that the Action continues to mis-cite the page number of the Yamamoto disclosure. That paper starts on page 823. It is the Schachter paper that contains a page 285.

B. Further Response

The Action has also failed to come to grips with the claimed recitation of a catalytic amount of an isolated nucleoside-diphospho fucose forming enzyme being present along with the isolated fucosyltransferase. As pointed out previously, GDP-fucose, the product of the former enzyme, can be an inhibitor of the fucosyltransferase under particular conditions. Schachter, who did not have both isolated enzymes together, faced no such potential problem of too much GDP-fucose and could therefore use as much enzyme as he could muster. It is thus further submitted that the present rejections should be withdrawn because no relied-on disclosure teaches or suggests the use of a catalytic amount of the nucleoside-diphospho fucose forming enzyme.

C. Summary

Each of the bases for rejection has been dealt with and overcome or otherwise made moot.

It is therefore believed that this application is in condition for allowance of all of the pending claims. An early notice to that effect is earnestly solicited.

No further fee or petition is believed to be necessary. However, should any further fee be needed, please charge our Deposit Account No. 23-0920, and deem this paper to be the required petition.

The Examiner is requested to phone the undersigned should any questions arise that can be dealt with over the phone to expedite this prosecution.

Respectfully submitted,

By _____
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Enclosures
Exhibit A
Form PTO-1449

CERTIFICATE OF MAILING

I hereby certify that this Reply and its stated enclosures are being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Mail Stop Amendments, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on January 19, 2006.

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Edward P. Gamson